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Antioxidant Micronutrients and Childhood Malignancy During Oncological Treatment

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Serum antioxidant vitamins A (retinol) and E (α-tocopherol), β-carotene, zinc, and selenium, and cholesterol and related proteins for 170 children with newly diagnosed malignancy were measured at diagnosis and 6 months after initiation of treatment, and compared with those of 632 cancer-free controls. Incident cancer cases and controls were 1–16 years old and recruited between 1986 and 1989. At diagnosis, age- and sex-adjusted serum concentrations of retinol, β-carotene, zinc, and α-tocopherol were significantly inversely associated with cancer. No significant decreases in mean values were observed at 6 months, except for the α-tocopherol–to–cholesterol ratio in patients with bone tumors and serum zinc in bone tumors and central nervous system malignancies. An increase during the period of treatment was found for retinol and selenium in leukemia patients. β-carotene was maintained at the initial concentrations determined prior to therapy. These findings provide further information about micronutrient requirements in children with cancer. Med. Pediatr. Oncol. 29:213–217, 1997.

Key words: vitamin status; childhood; malignancies; zinc; chemotherapy

INTRODUCTION

Cancer is frequently associated with a combination of metabolic abnormalities leading to a complex, abnormal biochemical state in the tumor-bearing host, including alterations in vitamin and mineral concentrations. Moreover, the tumoricidal action of several anti-cancer drugs is known to be mediated by a free radical dependent mechanism [1]. It has been suggested that lipid peroxidation is one of the main causes of irradiation damage. Conditioning regimens for cancer treatments in children often consist of high-dose chemotherapy, possibly combined with surgery or irradiation. These regimens may approach tolerance limit for several tissues. Vitamins and other micronutrients with antioxidant properties [2] have not been clearly assessed during childhood malignancies. We therefore investigated whether abnormal breakdown of antioxidants such as beta-carotene, alpha-tocopherol, zinc, and selenium occurs at the time of diagnosis and might follow the conditioning therapy in certain groups of children with cancer. The study was conducted in France as a satellite investigation of a large multicenter case-control survey designed to document the relationship between serum micronutrient values and childhood malignancy [3]. We therefore measured retinol (vitamin A), beta-carotene, alpha-tocopherol (vitamin E), cholesterol, zinc, selenium, and related proteins in serum collected from 1986 to 1989 from 170 children aged 1–16 years with newly diagnosed cancer, and from 632 healthy controls who were cancer free. In the patient group, sample processing was performed twice, once at diagnosis and before treatment (month 0), and once 6 months after initiation of treatment (month 6).

PATIENTS AND METHODS

Patients

The study group consisted of 170 eligible patients, with 82 males (48.2 percent) and 88 females (51.8 percent). Patients were distributed in five age groups: from 1 to 3 months (n = 6), from 4 to 11 months (n = 15), from 1 to 2 years (n = 20), from 3 to 5 years (n = 34), from 6 to 8 years (n = 25), from 9 to 11 years (n = 30), from 12 to 13 years (n = 20), and from 14 to 16 years (n = 20). Diagnosis was confirmed histologically in 90 percent of cases. The pilot study was conducted in France, in the cities and surrounding countryside of Paris (n = 30), Lyon (n = 30), Bordeaux (n = 20), Tours (n = 20), and Nancy (n = 70). The study group consisted

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TABLE I. Classification of Tumors in 170 Children Registered in the ''Cancer in Children and Antioxidant Micronutrients'' Study, France, 1986–1989, and Followed Up 6 Months After Initiation of Cancer Therapy, According to the Criteria of the International Classification Scheme for Childhood Cancer

Diagnostic group (ICD-0*)		n
I.	Leukemias	62
II.	Lymphoma and other reticuloendothelial neoplasma	24
III.	Central nervous system and miscellaneous intracranial and intraspinal neoplasms	20
IV.	Sympathetic nervous system tumours	10
V.	Retinoblastoma	1
VI.	Renal tumours (Wilms' tumour)	4
VII.	Malignant bone tumours	24
VIII.	Soft tissue sarcoma	16
IX.	Hepatic tumours (hepatoblastoma)	2
XII.	Other unspecified malignant neoplasms	7
All cancers		170

*International Classification of Diseases for Oncology.

of children admitted to 10 departments of pediatric oncology for diagnosis and cancer treatment between November 1, 1986, and November 30, 1989. Pathology departments notified the study team of all new reports of malignancies. The classification of tumors corresponds to the pathology and histology patterns of the malignant growth, and refers to the site of the primary tumor (International Classification of Diseases for Oncology, ICD-0) [4] (Table I).

A preoperative blood sample was obtained from the 170 patients before surgery, radiation, or chemotherapy were started. A second sample was collected from the same children 6 months after starting treatment. Concurrently, 632 healthy control subjects 0–16 years of age, 317 males (50.2 percent) and 315 females (49.8 percent), were recruited. The sampling procedure used has been described elsewhere and was conducted to provide a reference for age- and sex-related serum micronutrient concentrations for healthy French children [5–7]. Serum specimens from cancer patients and controls were grouped into sets to ensure that they would be analyzed together during the same period to avoid technical confounding factors between patients and controls. Serum specimens were identified by a number only to ensure that evaluators were blind to disease status.

Sample Processing

Blood was collected from fasting, seated individuals between 8 and 10 A.M. Blood samples were taken from a forearm vein into polystyrene-free zinc tubes, using steel needles. Serum was rapidly separated by centrifugation (1300 × g, 10 min). Separated 0.5 ml serum aliquots were removed and stored frozen at −70°C for up to 6 months until analysis.

Methods

A separate high-performance liquid chromatography assay comprising an isocratic system using silica gel (adsorption) as the stationary phase was used for retinol, alpha-tocopherol, and beta-carotene, as described previously [3,5]. Results for alpha-tocopherol were also expressed as ratio of serum vitamin E to cholesterol. The molar relation between retinol and retinol-binding protein (RBP) in serum was calculated to assess the vitamin A status. Retinol-binding protein and other serum protein values—immunoglobulins IgG, IgA, and IgM; two visceral proteins, namely, albumin and transthyretin (TTR); and two acute-phase reactants, alpha$_1$-acid glycoprotein (orosomucoid) and C-reactive protein (CRP)—were quantified by nephelometry [8]. Four of these parameters were aggregated in the following formula, allowing determination of a prognostic inflammatory and nutritional index (PINI) [9]:

$$\mathrm{PINI} = \frac{\text{alpha}_1\text{–acid glycoprotein (mg/l)} \times \text{C–reactive protein (mg/l)}}{\text{albumin (g/l)} \times \text{transthyretin (mg/l)}}$$

This tool should be of value in inflammatory and nutritional disorders, regardless of sex and age. Finally, a flame atomic absorption technique was used for plasma zinc determination [7,10], and selenium was assayed with a modification of the method described by Nève et al. [11].

Statistical Analysis

Since nutrient blood levels were generally skewed toward higher values, we used log-transformed variables which provided good approximations to the normal distribution. Means and standard deviations of chemistry variables were calculated for patients at month 0 before treatment began and for patients at month 6 after diagnosis and for controls. Data analysis was conducted with regression residual analysis after adjustment for age and sex on the basis of the control group data [3,5,6]. Statistical comparisons between groups were performed by means of t-tests and analysis of variance. First the average residual serum micronutrient and chemistry values for patients at month 0 were compared with the average residual value for the controls using the two sample t-tests. Data for patients at month 0 were subsequently compared with those reported for patients at month 6. Comparison was carried out separately for the different cancer sites. The statistical package SAS using the general linear modeling procedure (GLM) was used for the analysis [12].

RESULTS

Mean serum concentrations of retinol, beta-carotene, zinc, and alpha-tocopherol were lower in cancer patients

TABLE II. Mean (±Standard Deviation) or Median (Range) Serum Micronutrients and Biochemical Parameters in 170 Children with Malignancies, Before and After Cancer Therapy, ''Cancer in Children and Antioxidant Micronutrients'' Study, France, 1986–1989

Serum micronutrients	Controls (n = 632)	Pre-treatment	Post-treatment	*P* value
Retinol (μg/dl)	36 ± 12*	32 ± 16	39 ± 16	0.003
Retinol/RBP	0.83 ± 0.30*	0.71 ± 0.30	0.80 ± 0.32	NS
β-carotene (μg/l)	579 (206–812)*	390 (151–620)	397 (160–580)	NS
α-tocopherol (mg/dl)	8.8 ± 2.8*	7.3 ± 4.6	7.0 ± 3.0	NS
Cholesterol (g/l)	1.69 ± 0.46*	1.51 ± 0.47	1.58 ± 0.47	0.02
α-tocopherol/cholesterol	5.2 ± 1.3	4.9 ± 2.9	4.5 ± 1.7	NS
Zinc (μmol/l)	14.6 ± 3.1*	13.4 ± 4.0	11.5 ± 3.1	0.004
Selenium (μmol/l)	0.81 ± 0.34	0.77 ± 0.30	0.77 ± 0.26	NS
IgG (g/l)	14.0 ± 5.3	12.3 ± 6.5	11.0 ± 5.5	0.002
IgA (g/l)	1.8 ± 1.2	2.2 ± 1.6	1.9 ± 1.7	<0.001
IgM (g/l)	2.4 ± 1.5	3.0 ± 1.9	1.5 ± 1.4	<0.001
Albumin (g/l)	53 ± 11*	38 ± 10	43 ± 10	<0.001
Transthyretin (mg/dl)	27 ± 10*	20 ± 11	26 ± 12	<0.001
α_1-acid glycoprotein (mg/dl)	122 ± 51*	170 ± 103	105 ± 60	<0.001
Retinol-binding protein (mg/dl)	3.5 ± 1.2	3.3 ± 1.7	3.9 ± 1.9	<0.001
C-reactive protein (mg/dl)	0.83 (0.30–1.35)*	2.53 (1.98–5.56)	1.64 (1.18–4.65)	0.003
PINI	0.9 (0.1–1.8)	20.0 (4.2–40.1)	4.1 (2.2–18.9)	0.004

*$P < 0.001$ for significant t-test between age and sex adjusted healthy controls and pretreatment cases

at month 0 than in controls (Table II). Since the levels of cholesterol tended to be very significantly lower in patients than in controls and were positively associated with vitamin E values in controls ($P < 0.001$), the ratio of vitamin E to cholesterol tended to diminish and suppress the significant difference. There was no appreciable difference in serum selenium concentrations. It should be noted that variability, as indicated by the standard deviation relative to the mean, was high for CRP and the PINI determined by the above-mentioned formula, particularly in patients.

The PINI score was below 1.5 in healthy controls and its mean value was around 20 in patients at diagnosis [9]. There were no appreciable differences between patients and controls for Ig and retinol-binding protein, revealing a wider scatter range than that of albumin. Absolute means for albumin and transthyretin levels were lower for overall cancers than in controls, and higher for CRP and alpha$_1$-acid glycoprotein, recognized to be a sensitive marker of the phlogistic phenomenon. The changes in mean values of the micronutrient status parameters for all childhood cancers and for types of malignancy for each cancer site are given in Tables II–IV. It is obvious from Table II that children in the ''all cancers'' group showed an increase in serum retinol and serum visceral proteins, albumin, transthyretin, and retinol-binding protein, and a decrease in levels of acute phase reactants after 6 months of treatment, whereas beta-carotene and alpha-tocopherol values remained unchanged and low in comparison with the initial value. Some significant differences between diagnosis and month 6 were also found according to the cancer site. Patients with leukemia tended to have higher retinol, molar retinol–to–retinol-binding protein ratio, cholesterol, and selenium levels after 6 months of treatment. Patients with malignant lymphoma, who were treated during the whole observation period with combined cytostatic therapy, tended to have increased retinol levels than at diagnosis. No significant decreases in mean values were observed. Patients with brain tumors had lower zinc levels, with a slightly significant decrease in inflammation parameters in comparison with the initial values. For patients with bone tumors, a decrease in serum alpha-tocopherol to cholesterol ratio and in zinc was found during the period of treatment.

DISCUSSION

Recognition of the fact that nutritional requirements may be altered in a complex way by the development of malignant disease is of practical significance. Radiotherapy and aggressive oncological chemotherapy frequently affect the nutritional status of tumor patients. The effects of the cytostatic agents on the tumor-bearing host seem to overcome the physiological protein-sparing mechanisms [13,14]. There is little evidence to point out that specific deficiencies in vitamins and minerals exist in cancer. Nevertheless, deficiencies are part of a total picture of malnutrition.

In general, the vitamin indicators measured in this report were in a lower range than the range of the control group. The mean values of beta-carotene, retinol, alpha-tocopherol, zinc, and the related nutritional proteins were lower at the beginning of the observation period in comparison with controls.

No significant decreases in mean values were observed at 6 months, except for the alpha-tocopherol–to-

TABLE III. Absolute Mean (±Standard Deviation) or Median (Range) Serum Levels Among Children With Cancer, France, 1986–1989

	Leukemia (n = 62)		Lymphoma (n = 24)	
Nutrient	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Retinol (μg/dl)	28 ± 15	45 ± 19[a]	29 ± 11	32 ± 10
Retinol/RBP	0.67 ± 0.26	0.79 ± 0.36	0.68 ± 0.29	0.76 ± 0.22
β-carotene (μg/l)	414 (120–650)	308 (110–550)	395 (95–570)	361 (85–550)
α-tocopherol (mg/l)	8.2 ± 6.4	6.6 ± 2.9	7.1 ± 2.8	7.1 ± 3.3
Cholesterol (g/l)	1.36 ± 0.43	1.52 ± 0.52[a]	1.47 ± 0.39	1.56 ± 0.43
α-tocopherol/Cholesterol	5.9 ± 3.9	4.4 ± 1.8	4.9 ± 2.3	4.6 ± 1.8
Selenium (μmol/l)	0.68 ± 0.27	0.81 ± 0.28[a]	0.68 ± 0.28	0.66 ± 0.19
Zinc (μmol/l)	12.5 ± 3.9	11.3 ± 3.7	13.3 ± 3.2	12.1 ± 2.3
IgG (g/l)	11.7 ± 5.3	9.8 ± 5.1	14.2 ± 10.4	10.0 ± 4.3
IgA (g/l)	2.0 ± 1.4	1.4 ± 1.0	2.4 ± 1.8	1.6 ± 1.1[a]
IgM (g/l)	2.6 ± 1.7	1.0 ± 1.1[a]	3.2 ± 2.2	1.4 ± 1.0
Albumin (g/l)	37 ± 9	42 ± 10	39 ± 11	40 ± 9
Transthyretin (mg/dl)	16 ± 8	27 ± 12[a]	18 ± 10	22 ± 8
RBP (mg/dl)	3.0 ± 1.6	4.4 ± 2.0[a]	3.2 ± 1.6	3.4 ± 1.5
α_1-acid glycoprotein (mg/dl)	182 ± 104	103 ± 54[a]	169 ± 102	107 ± 54
CRP (mg/dl)	2.90 (2.30–5.55)	1.78 (1.20–3.55)	2.57 (2.10–5.26)	1.23 (1.26–1.40)
PINI	24 (15–40)	4 (2–12)	21 (16–50)	2 (1–5)

[a]$P < 0.001$ for significant t test against pretreatment controls

TABLE IV. Absolute Mean (±Standard Deviation) or Median (Range) Serum Levels Among Children With Cancer, France, 1986–1989

	Central nervous system (n = 20)		Malignant bone tumours (n = 24)	
Nutrient	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Retinol (μg/dl)	46 ± 17	47 ± 17	34 ± 11	33 ± 10
Retinol/RBP	0.80 ± 0.21	0.89 ± 0.31	0.92 ± 0.47	0.89 ± 0.39
β-carotene (μg/l)	407 (115–676)	486 (140–654)	316 (81–505)	361 (110–578)
α-tocopherol (mg/l)	6.9 ± 3.2	7.6 ± 3.4	7.5 ± 3.4	7.1 ± 3.2
Cholesterol (g/l)	1.79 ± 0.42	1.89 ± 0.45	1.56 ± 0.38	1.61 ± 0.35
α-tocopherol/Cholesterol	3.8 ± 1.8	4.1 ± 1.5	4.9 ± 1.8	4.3 ± 1.8[a]
Selenium (μmol/l)	0.90 ± 0.31	0.86 ± 0.28	0.83 ± 0.22	0.75 ± 0.29
Zinc (μmol/l)	14.1 ± 3.0	11.2 ± 1.9[a]	14.7 ± 3.8	11.8 ± 1.9[a]
IgG (g/l)	9.9 ± 3.4	8.8 ± 4.5	16.9 ± 6.4	14.6 ± 4.9
IgA (g/l)	1.8 ± 1.1	1.5 ± 1.0	3.5 ± 2.4	3.3 ± 2.6
IgM (g/l)	3.2 ± 1.8	2.0 ± 1.1[a]	4.1 ± 2.8	2.0 ± 0.9
Albumin (g/l)	38 ± 8	44 ± 12	44 ± 9	46 ± 12
Transthyretin (mg/dl)	30 ± 11	33 ± 14	25 ± 10	28 ± 13
RBP (mg/dl)	4.3 ± 1.7	3.8 ± 1.2	3.1 ± 1.5	3.3 ± 2.1
α_1-acid glycoprotein (mg/dl)	137 ± 65	83 ± 48[a]	203 ± 144	107 ± 37[a]
CRP (mg/dl)	1.60 (1.20–2.45)	1.26 (0.41–2.55)	3.02 (1.28–5.56)	1.48 (0.55–2.93)
PINI	7 (3–15)	2 (1–5)	20 (16–40)	2 (1–4)

[a]$P < 0.001$ for significant t test against pretreatment controls

–cholesterol ratio in patients with bone tumors and serum zinc in bone tumors and central nervous system malignancies. Indeed, an increase in mean values for some parameters was found during the period of treatment, namely for retinol and selenium in leukemia patients. The status for other nutrients in these patients was not affected. Beta-carotene was maintained at the initial concentrations determined prior to therapy.

Obviously, if the antioxidant properties of beta-carotene, zinc, and vitamin E are taken into account, the disturbances described in central nervous system and bone tumors may suggest a loss of antioxidants in patients undergoing therapy. There may be multifactorial causes for loss of antioxidants in patients undergoing cancer treatment. The tumoricidal action of several anticancer drugs and radiation is believed to be mediated by an oxygen-free radical dependent mechanism [1]. Activated granulocytes appearing during hematopoietic reconstitution may serve as a source of oxygen radicals, in combination with impairment of iron storage and release during chemotherapy [15,16]. Moreover, in view of the decrease in zinc and vitamin E parameters observed in some cancer groups and the maintenance of low levels of beta-carotene in the ''all cancer'' group, the results sug-

gest that intake of nutrients was insufficient. In such situations, the present daily recommended dietary allowance for alpha-tocopherol (RDA: 8 mg, or 10 mg tocopherol equivalents) usually provided by the amounts of vitamin E administered in nutritional therapy procedures, may be too low [17].

Nevertheless, the vitamin and nutritional status of the groups of children with cancer investigated appeared in general to be adequate, even during intensive treatment or diseases imposing prolonged chemotherapy. Moreover, the conditioning treatment was related to improvement in the balance between the occurrence of malnutrition and inflammation, with increase in serum albumin and transthyretin levels, 2 substances used as markers of nutritional status, in view of the link between hepatic synthesis and substrate availability related to nutritional status [13]. The improvement in serum retinol concentration, independent of beta-carotene, suggests characteristics of the vitamin separate from carotene. However, special attention should be paid to other micronutrients, as other fat-soluble vitamins [18], vitamin B12 and folic acid [19], have been found to be decreased during treatment of cancer patients.

In conclusion, supplementation with antioxidants, even at a level higher than that administered in enteral or parenteral (for zinc) nutrition, could be required in patients undergoing highly toxic cancer treatment. Ongoing intervention with nutrients including beta-carotene, alpha-tocopherol, and trace minerals, e.g., zinc, should lead to more effective maintenance of optimal nutrition and retention in children with cancer, according to different patterns of tumor excision, radiation therapy, and chemotherapy.

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